IN THE CLAIMS

36. (Amended) An isolated nucleic acid having a nucleotide sequence encoding an amino acid sequence depicted in Figure 4, SEQ ID NO: 2, which is flanked by a heterologous sequence.

45. (Amended) An isolated nucleic acid having a nucleotide sequence encoding an amino acid sequence comprising amino acids 1-45 of Figure 4, SEQ ID NO:2.

REMARKS

I. Status of the Claims

Claims 27-61 are pending. Claims 27-44 have been allowed. Claim 36 has been amended to insert a comma after the terms "Figure 4" in the interest of clarity. Claim 45 has been amended to clarify that the sequence is a "nucleotide" sequence.

II. Withdrawal of Claims 50-61

The Examiner has withdrawn claims 50-61 from consideration contending that they are drawn to the invention Group III, and are distinct from the elected invention of Group I for the reason of record, see paper 4, dated 9/3/98.

This withdrawal is respectfully traversed, and rejoinder is requested.

Claims 50-61 are directed to a method of using a cell that expresses a novel hERβ as a result of comprising a DNA vector of the invention. To the extent that the nucleic acid, vector and cell line compositions of matter are novel and nonobvious, the methods of using these composition in a biotechnological process of screening for ligands is also novel and nonobvious. 35 U.S.C. §103(b)(1)(A).[1] Thus, claims 50-61 are directed to a method of using a product produced by a process of genetically altering an organism to express an exogenous nucleotide sequence. 35 U.S.C. §103(b)(3)(A) and (C).

Furthermore, "if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined (MPEP 821.04). Applicant provisionally elected claims 1-16 (new claims 27-44) directed to the product in the amendment filed October 5, 1998. Product claims 27-44 were subsequently found allowable in the Final Office Action mailed June 6, 2001. Withdrawn process claims 50-61 contain all the limitations of the allowable product claims. Therefore, rejoinder is appropriate in this case.

---

[1]The composition of matter and process were owned by the same person or subject to an obligation of assignment to the same person at the time they were invented. 35 U.S.C. §103(b)(1)(B).

III. **Rejection under 35 U.S.C § 112, first paragraph**

Claims 45-49 have been rejected under 35 U.S.C § 112, first paragraph as non-enabled. The Examiner contends that the specification does not reasonably provide enablement for nucleic acids comprising a sequence encoding an amino acid sequence consisting of amino acids 1-45 of SEQ ID NO:2 and vectors encoding the fusion protein and cells comprising the fusion protein. Specifically, the Examiner asserts that the specification fails to provide sufficient information on the function of the fragment encoding amino acids 1-45 of SEQ ID NO:2, such as definitive structural features and their relationship to function.

This rejection is respectfully traversed and reconsideration is requested.

Claims 45-49 recite structure, not a function as the Examiner appears to be suggesting. The polypeptides encoded by the claimed nucleic acids have utility, e.g., for generating antibodies. One advantage of such antibodies would be their ability to specifically bond to the novel estrogen-β receptor of the invention. The specification at page 22, lines 13 to page 24, line 3 describes making antibodies, and beginning on page 24, line 5 describes the application of using such antibodies to identify compounds that interact with hERβ. Furthermore, the invention also encompasses methods for identifying hERβ-interactive compounds, including agonists, antagonists, and co-activators (see page 35, lines 8-10).

Also, with respect to claims 45-49, the Examiner further contends that the instant disclosure of a single distinct polypeptide, and nucleic acid encoding said

polypeptide, does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length, truncated, mutated, variant and fusion proteins encoded by the disclosed nucleic acids.

Applicants respectfully traverse this contention. Given any useful polypeptide, and the nucleic acid encoding it, one of ordinary skill in the art is enabled to generate numerous constructs comprising such polypeptide, including full length estrogen β receptors, fusion proteins, or polypeptide fragments. The claimed protein is, in this respect, no different from any other patentable product, such as a chemical (which might find itself in any number of compositions and formulations, whether or not envisioned by the inventor of the chemical), or an electronic transistor (which might be included in a hand-held radio, an automobile, or an interplanetary space vehicle, whether or not envisioned by the inventor). This claim provides the inventors with rights to what is properly theirs: an isolated nucleic acid having a nucleotide sequence encoding an amino acid sequence comprising amino acids 1-45 of Figure 4 (SEQ ID NO: 2), whatever other components may be present.

The Examiner properly should not dispute that the 1-45 sequence is useful. At the time this invention was made, the ordinary skilled artisan, given any polypeptide and any nucleic acid encoding it, could engineer a multitude of constructs comprising the polypeptide. To argue otherwise ignores the abundant literature describing a multitude of fusion products, as well as the plethora of commercial vectors that permit expression of polypeptide fusion proteins -- perhaps foremost

among them the yeast two-hybrid system. Enumeration of all these systems at this point in time necessitates unending pages and exhibits. Applicants believe the Examiner is well aware of the literature and that such products are commercially available. The Federal Circuit recognized that generating fusion constructs was state of the art in 1976: "translation of a ribosmal DNA -- which is not normally translated -- in a fusion protein with β galactosidase established with a reasonable expectation of success that one could express any protein this way." *See In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1678-9 (Fed. Cir. 1988) (discussing a 1976 prior art reference). However, some additional fusion protein systems (besides full length β estrogen receptor, the 1-45 fragment, and an O'Farrell-type β galactosidase fusion) are noted:

1. Y2H technology is based on the fact that proteins can be considered modularly. The modules fold independently and, as protein function depends on folding, the modules can function independently.

2. Phage display is another powerful technique which is fundamentally based on the ability of protein modules to fold and function independently. Antibody domains are routinely displayed on phage and retain their binding activity. Perhaps even more relevant is surface display as this involves fusion to TM proteins. Stahl & Uhlen (1997) *TIBTECH* 15:185-192, attached hereto as Exhibit A, reports that enzymes, which require proper folding for activity, had been displayed in active form on bacterial cell surfaces as fusion proteins. It admits that

success is not guaranteed, but the only failure which it reports arose from incorrect targeting (periplasmic retention) rather than from a lack of enzymatic activity.

3. Hybrid membrane proteins. Ellis *et al.* (1986) *PNAS USA* 83:8137-41, attached hereto as Exhibit B, reported that the extracellular domains of the human insulin receptor could be fused to heterologous TM and cytoplasmic domains (from a bacterial chemoreceptor) and retain function (insulin binding and uptake, insulin affinity, oligomeric formation, conformational epitopes). Similar work has been reported for growth hormone receptor (GHR) (Ishizaka-Ikeda et al. (1993) *PNAS USA* 90:123-7); attached hereto as Exhibit C. The extracellular domain from the GHR was substituted into the GCSF receptor either on its own, with its TM region or with its TM region + par of its cytoplasmic region. Each of these modified GCSF receptors acquired the ability to bind to growth hormone.

4. Green fluorescent protein (GFP) is widely used for reporting expression because it is easily visualized. It is used as a fusion partner- to study the expression of a particular protein, GFP is fused to it. There are many examples where GFP has been fused to eukaryotic (including mammalian) proteins without inhibiting their function. The following are examples: Sidorova *et al.* (1995) *Mol Biol Cell* 6:1641-58 (Exhibit D); Hampton *et al.* (1996) *PNAS USA* 93: 828-33 (Exhibit E). In all cases, GFP activity was retained as was the activity of the protein being studied *i.e.* both domains in the fusion protein retained activity.

5. Immunoglobulin domains. Antibodies come in various classes, including soluble IgG and membrane-bound IgM. Variable domains can be swapped between different classes without affecting antigen recognition. This is a basic example of protein modularity and shows that (a) single active domains can tolerate various different fusion partners (b) soluble or membrane-bound fusion partners can be equally tolerated.

6. T-bodies date back to 1989 and are chimeric receptor proteins consisting of an extracellular binding domain from an antibody and the TM and cytoplasmic domains from T cell receptor (TCR). When a peptide binds to a native TCR, the conformational change is transmitted across the membrane to the cytoplasmic domain, which initiates a cell response mechanism. In a T-body, however, the TCR peptide-binding domain is replaced by the antigen-binding domain from an antibody. When the antigen and antibody interact, the T-body retains the ability to signal to the cytoplasmic domain. The modular nature of the TCR allows its functional domains to be swapped in this way and this is a further example that a single active domain (e.g. an immunoglobulin domain) can tolerate a variety of different fusion partners. See Finney *et al.* (1998) *J. Immunol.* 161: 2791-97 (Exhibit F).

7. Gene trapping vectors. The "secretory trap" of Skarnes *et al.* (1995) *PNAS USA* 92:6502-6596 (Exhibit G) is based on the fact that β-galactosidase retains its activity in a multi-domain transmembrane protein (targeting sequence, cytoplasmic domain, TM domain, β-galactosidase domain, neomycin

phosphotransferase domain, polyadenylation signal). β-galactosidase was found to lose its activity when under the control of a targeting sequence which directed its translocation as a fusion into the lumen of the endoplasmic reticulum (ER), but this did not occur when a TM sequence was included such that the β-galactosidase was tethered to the ER membrane in the cytosol. β-galactosidase can thus retain its activity when expressed as a membrane-bound fusion protein.

8. Standard molecular biology reagents. Invitrogen sells a vector called *pDisplay* which is described as follows:

> pDisplay™ is a mammalian expression vector that is designed to target recombinant proteins to the surface of mammalian cells. Displayed proteins can be analyzed for the ability to interact with known or prospective ligands. Proteins of interest are targeted and anchored to the cell surface by cloning the gene of interest in frame with pDisplay's unique N-terminal cell surface targeting signal and the C-terminal transmembrane anchoring domain of platelet derived growth factor receptor. In contrast to phage display vectors which operate exclusively in prokaryotic cells, pDisplay™ offers the advantage of having the displayed protein of interest processed in mammalian cells. Therefore, recombinant proteins of eukaryotic origin that are expressed from pDisplay™ more closely resemble their native form.
>
> Expression of a recombinant protein in mammalian cells as a surface-exposed active fusion is therefore now available off the shelf. The vector is sold in the expectation that the protein will be tethered and displayed without losing activity.

In light of the foregoing remarks, Applicants respectfully request withdrawal of this rejection.

In view of the above amendment and remarks, all of the pending claims are now believed to be in condition for allowance. Allowance of all the pending claims is earnestly solicited.

The Examiner and United States Patent and Trademark Office are urgently requested to note the following:

Mailing Address

The Office Action dated June 6, 2001 was misdirected and sent to American Home Products. In accordance with the Declaration and Power of Attorney on file, all correspondence has previously, and should continue to be, sent to:

Darby & Darby, P. C.

805 Third Avenue

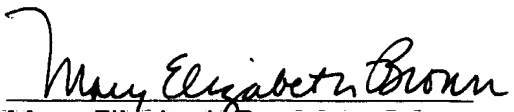
New York, New York 10022

Customer Number 07278

All telephone calls should be directed to Paul F. Fehlner, Ph.D. at (212) 527-7700 in accordance with 37 C.F.R. §1.34(a)

The United States Patent and Trademark Office's failure to transmit correspondence to the correct address has and will result in unacceptable delays.

Respectfully submitted,



Mary Elizabeth Brown
Reg. No. 46,579
Attorney for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

::ODMA\WORLDOX\M:\0646\0D205\MEB0323.WPD

EXPRESS MAIL CERTIFICATE

Date 9/5/01 Label No. EL767724305US

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

A. DiLullo A. DiLullo

Name (Print) Signature

PLEASE CHARGE ANY DEFICIENCY UP TO $300.00 OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100

Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No: 0646/0D205

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ramesh A. Bhat

Serial No.: 08/906,365 Art Unit: 1646

Confirmation No.:

Filed: Auguest 5, 1997 Examiner: N. Basi

For: Novel Human Estrogen Receptor-Beta

MARK-UP FOR AMENDMENT PURSUANT TO 37 CFR 1.121

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

September 5, 2001

Claims:

36. An isolated nucleic acid having a sequence encoding an amino acid sequence depicted in Figure 4, SEQ ID NO:2, which is flanked by a heterologous sequence.

45. An isolated nucleic acid having a nucleotide sequence encoding an amino acid sequence [consisting of] comprising amino acids 1-45 of Figure 4, SEQ ID NO:2.